

## I. AMENDMENT TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

### LISTING OF CLAIMS

Claim 1. (currently amended) A method of effectively treating hypertension, angina, or both conditions in a human patient, comprising:  
administering felodipine transdermally to the human patient by applying a transdermal delivery system containing felodipine to the skin of the patient, and maintaining said transdermal delivery system in contact with the skin of said patient for at least 3 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said felodipine within 36 hours from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the three-day dosing interval,

said transdermal delivery system having a mean relative release rate of from about 4.2  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 20.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 24 hours;

from about 3.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 14.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 48 hours; and

from about 2.7  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 10.8  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water;

said transdermal delivery system providing a mean relative release rate of felodipine to provide a plasma level of felodipine of at least 0.1 ng/ml within about 6 hours after application of said transdermal delivery system onto the skin of said patient.

Claim 2. (canceled)

Claim 3. (original) The method of claim 1, further comprising maintaining a plasma level of felodipine at steady-state from about 1.0 to about 3.0 ng/ml.

Claim 4. (original) The method of claim 1, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 5. (original) The method of claim 1, wherein said transdermal delivery system has a mean relative release rate from about 0.5  $\mu\text{m}/\text{hour}/\text{cm}^2$  to about 25  $\mu\text{m}/\text{hour}/\text{cm}^2$  of said transdermal delivery system.

Claim 6. (canceled)

Claim 7. (original) The method of claim 1, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63  $\mu\text{g}/\text{cm}^2$  to about 388  $\mu\text{g}/\text{cm}^2$  at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claim 8. (currently amended) A The method of claim 1 ~~effectively treating hypertension, angina, or both conditions in a human patient, comprising:~~  
~~administering felodipine transdermally to the human patient by applying a transdermal delivery system containing felodipine to the skin of a patient, and maintaining said~~  
wherein said transdermal delivery system is maintained in contact with the skin of the patient for at least 5 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said felodipine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

Claim 9. (original) The method of claim 8, wherein the plasma level of felodipine at 48 hours does not decrease by more than 30% over the next 72 hours.

Claim 10. (original) The method of claim 8, further comprising maintaining an effective mean relative release rate of said transdermal delivery system to provide a substantially first order plasma level increase of felodipine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of felodipine until the end of at least the five-day dosing interval.

Claim 11. (canceled)

Claim 12. (original) The method of claim 8, further comprising maintaining a plasma level of felodipine at steady-state from about 1.5 to about 2.3 ng/ml.

Claim 13. (original) The method of claim 8, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 14. (currently amended) The method of claim 8, wherein said transdermal delivery system has a mean relative release rate from about  $0.5 \mu\text{m}/\text{hour}/\text{cm}^2$   $\mu\text{g}/\text{hour}/\text{cm}^2$  to about  $25 \mu\text{m}/\text{hour}/\text{cm}^2$   $\mu\text{g}/\text{hour}/\text{cm}^2$  of said transdermal delivery system.

Claim 15. (currently amended) The method of claim 8, wherein said transdermal delivery system has ~~a mean relative release rate from about  $4.2 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $20.0 \mu\text{g}/\text{cm}^2/\text{hr}$  at 24 hours; from about  $3.3 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $14.0 \mu\text{g}/\text{cm}^2/\text{hr}$  at 48 hours; and from about  $2.7 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $10.8 \mu\text{g}/\text{cm}^2/\text{hr}$  at 72 hours; and~~ a mean relative release rate of from about  $2.4 \mu\text{g}/\text{cm}^2/\text{hr}$  to about  $8.9 \mu\text{g}/\text{cm}^2/\text{hr}$  at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claim 16. (original) The method of claim 8, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about  $63 \mu\text{g}/\text{cm}^2$  to about

388  $\mu\text{g}/\text{cm}^2$  at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  at 72 hours; and from about 231  $\mu\text{g}/\text{cm}^2$  to about 850  $\mu\text{g}/\text{cm}^2$  at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claims 17-19 (canceled)

Claim 20. (currently amended) A transdermal delivery system containing felodipine or a pharmaceutically acceptable salt thereof which provides a mean relative release rate of from about 4.2  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 20.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 24 hours;

from about 3.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 14.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 48 hours; and

from about 2.7  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 10.8  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water provides a mean relative release rate from about 0.5  $\mu\text{m}/\text{hour}/\text{cm}^2$  to about 25  $\mu\text{m}/\text{hour}/\text{cm}^2$  of said transdermal delivery system;

said transdermal delivery system providing a plasma level of felodipine of at least about 0.1 ng/ml by about 6 hours after application of said transdermal delivery system onto the skin of the a human patient; said transdermal delivery system maintaining a therapeutic blood level until the end of at least a three-day dosing interval and said transdermal delivery system maintaining a plasma level of felodipine at steady-state from about 0.1 to about 3.3 ng/ml.

Claim 21. (canceled)

Claim 22. (original) The transdermal delivery system of claim 20, which provides an in-vitro cumulative amount of permeation of from about 63  $\mu\text{g}/\text{cm}^2$  to about 388  $\mu\text{g}/\text{cm}^2$  at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  at 72 hours; and from about 231  $\mu\text{g}/\text{cm}^2$  to about 850  $\mu\text{g}/\text{cm}^2$  at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell

where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claim 23. (original) The transdermal delivery system of claim 20, comprising a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer by weight comprising 20 to 90% of a polymeric matrix, 0.1 to 30% of a softening agent, 0.1 to 20% of felodipine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% of a solvent for the felodipine or salt thereof.

Claim 24. (original) The transdermal delivery system of claim 20, which is a laminated composite comprising (a) a polymer backing layer that is substantially impermeable to felodipine or the pharmaceutically acceptable salt thereof; and (b) a reservoir layer comprising an acrylate or silicon based pressure-sensitive adhesive, 0.1 to 20% of felodipine base or of a pharmaceutically acceptable salt thereof, 0.1 to 30% of an ester of a carboxylic acid acting as a softening agent and 0.1 to 30% of a solvent for felodipine having at least one acidic group.

Claim 25. (original) The transdermal delivery system of claim 20, which maintains a plasma level of felodipine at steady-state from about 1.5 to about 2.3 ng/ml.

Claim 26. (currently amended) ~~A~~ The transdermal delivery system of claim 20, wherein comprising felodipine or a pharmaceutically acceptable salt thereof which maintains an effective mean relative release rate to provide a therapeutic blood level of said felodipine within three days from the initiation of the dosing interval, and thereafter maintaining said transdermal delivery system maintains a therapeutic blood level until the end of at least ~~the~~ a five-day dosing interval.

Claim 27. (canceled)

Claim 28. (currently amended) The transdermal delivery system of claim ~~25~~ 26, which maintains a plasma level of felodipine at steady-state from about 1.5 to about 2.3 ng/ml.

Claim 29. (canceled)

Claim 30. (currently amended) The transdermal delivery system of claim ~~25~~ 26, wherein said transdermal delivery system has a mean relative release rate from about 0.5  ~~$\mu\text{m}/\text{hour}/\text{cm}^2$~~   $\mu\text{g}/\text{hour}/\text{cm}^2$  to about 25  ~~$\mu\text{m}/\text{hour}/\text{cm}^2$~~   $\mu\text{g}/\text{hour}/\text{cm}^2$  of said transdermal delivery system.

Claim 31. (currently amended) The transdermal delivery system of claim ~~25~~ 26, wherein said transdermal delivery system has a mean relative release rate from about 4.2  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 20.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 24 hours; from about 3.3  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 14.0  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 48 hours; and from about 2.7  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 10.8  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 72 hours; and a mean relative release rate from about 2.4  $\mu\text{g}/\text{cm}^2/\text{hr}$  to about 8.9  $\mu\text{g}/\text{cm}^2/\text{hr}$  at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claim 32. (currently amended) The transdermal delivery system of claim ~~25~~ 26, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63  $\mu\text{g}/\text{cm}^2$  to about 388  $\mu\text{g}/\text{cm}^2$  at 24 hours; from about 105  $\mu\text{g}/\text{cm}^2$  to about 660  $\mu\text{g}/\text{cm}^2$  at 48 hours; and from about 139  $\mu\text{g}/\text{cm}^2$  to about 854  $\mu\text{g}/\text{cm}^2$  at 72 hours; and from about 231  $\mu\text{g}/\text{cm}^2$  to about 850  $\mu\text{g}/\text{cm}^2$  at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of Ethanol:water.

Claim 33. (original) The transdermal delivery system according to claim 23, wherein the backing layer is composed of a flexible material.

Claim 34. (original) The transdermal delivery system according to claim 23, wherein the backing layer is selected from the group consisting of a flexible material, an inflexible material, and an aluminum foil.

Claim 35. (currently amended) The transdermal delivery system according to claim 23, wherein the polymeric matrix is at least one of rubber, a ~~rubber-like~~ synthetic homo-, co- or blockpolymer, a urethane and silicone.

Claim 36. (original) The transdermal delivery system according to claim 23, wherein the softening agent is at least one of dodecanol, undecanol, octanol, a glycol and glycanol.

Claim 37. (original) The transdermal delivery system according to claim 23, wherein the solvent is a monoester of a dicarboxylic acid.

Claim 38. (original) The transdermal delivery system according to claim 23, wherein the solvent is at least one of monomethyl glutarate and monomethyl adipate.

Claim 39. (canceled)

Claim 40. (original) The transdermal delivery system according to claim 23, wherein by weight the polymer is present in about 55%, the felodipine in about 10%, the solvent in about 10% and the softener in about 15%.

Claim 41. (original) A transdermal delivery system according to claim 23, wherein the solvent is present in from about 25 to 100% the weight of the felodipine.

Claim 42. (original) The transdermal delivery system according to claim 23, which also comprises a removable protective layer.

Claim 43. (original) The transdermal delivery system according to claim 23, wherein the

pressure-sensitive adhesive reservoir layer comprises a polymer based on an acrylate, a methacrylate, a silicon compound or a combination thereof.

Claim 44. (previously presented) The transdermal delivery system according to claim 23, wherein the softening agent is a medium-chain triglyceride of the caprylic/capric acids of coconut oil.

Claim 45. (original) The transdermal delivery system according to claim 23, wherein the solvent has at least one acidic group.

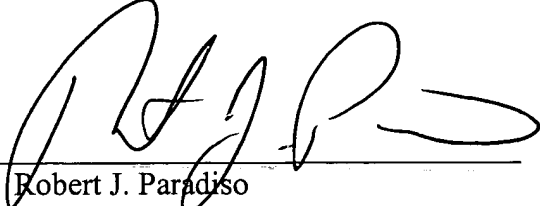


This response is being submitted within 30 (thirty) from the date of the Notice of Non-Compliant Amendment. Accordingly, no fee is believed due. If it is determined that any fees are due, the Commissioner is hereby authorized to charge any deficiencies to Attorney Deposit Account No. 50-0552.

Respectfully submitted,

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